Remarks

Claims 1, 3-15, and 17-39 are currently pending in the application. Claims 5, 6, 24, 26, 28-34, and 36-39 are withdrawn. Claims 1, 3-4, 7-15, 25, 27, and 35 currently stand rejected. Claim 17 is cancelled. Claims 1, 3-6, 7, 8, 18, 21, and 23 are amended. Support for the amendment to claims 1, 8, 18, 21, and 23 is found in original claim 17. Support for the amendment to claim 3 is found in pargraph [0043] of the application as filed. Claims 4 and 7 are amended to correct typographical errors. The rejections levied in the Office Action are addressed individually below.

1. Rejections under 35 U.S.C. § 112, 2nd paragraph. Claims 1, 3-4, 7-15, 17, 20-23, 25, 27, and 35 are rejected under 35 U.S.C. § 112, 2nd paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner states that for claim 1 "it is unclear what compounds are encompassed within a disulfide-substituted aryl moiety [. . .] the instant specification does not fully define what is meant by a moiety." The Examiner also considers other instances of the term "moiety" in claims 1 and 17 to be indefinite. Applicant respectfully disagrees and submits that the recitation of the term "moiety" does not render the instant claims indefinite.

Applicant respectfully points out that the term "moiety" is used widely in the patent literature, and its definition in the context of the chemical arts is well understood. In fact, Applicant respectfully submits that Examiner Ha is well aware of the metes and bounds of the term "moiety," as demonstrated by the Examiner's recent allowance of the following claim in U.S. Pat. No. 7,414,106 ("the '106 patent"):

> 1. A method of cleaving a peptide from solid phase comprising: providing a protected peptide linked to a solid phase having a hydrazide linker; oxidizing said hydrazide linker with an oxidizer to form a solid phase peptide having an acyl diazene functional group or ***moiety***, wherein said oxidizer and said solid phase peptide are present in a ratio, and cleaving said acyl diazene functional group or ***moiety*** with a cleaving agent, wherein said cleaving agent is an alpha amino acid thioester (emphasis added by Applicant).

Not only did Examiner Ha allow the recitation of the term "moiety" in the claims of the '106 patent (and despite the specification failing to define the term), the term was added to the claims via an Examiner's amendment (see Notice of Allowability, dated April 18, 2008).

Moreover, the Examiner seems to think that a "moiety" can be any portion of a molecule, thereby leading the Examiner to interpret "aryl moiety" to mean a piece of an aryl compound. With such an interpretation, an "aryl moiety" could encompass hydrogen. Applicant respectfully submits that no chemist would interpret the term in this manner. Rather, the term "aryl moiety" means a part of a compound, which part is aryl.

For all of these reasons, Applicant submits that the term is definite. Nevertheless, solely in order to expedite prosecution of this case, Applicant has amended the claims to remove the term. Applicant respectfully requests that the rejection be removed.

2. **Rejection under 35 U.S.C. § 112, 1st paragraph.** Claims 1-3, 8-15, 17-23, 25, and 27 are rejected under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the written description requirement. In response to the Examiner's assertion that the "specification does not describe any other A1, and A2 that are aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl group," Applicant expresses disappointment that the Examiner did not respond to Applicant's arguments set forth in the response dated December 17, 2008 (see page 17, first full paragaph). Applicant respectfully requests that the Examiner provide explicit reasoning as to why amino acid side-chain groups do not satisfy the definitions of aliphatic, heteroaliphatic, aromatic, or heteroaromatic.

The Examiner appears to find the term "moiety" to be problematic in the context of A1 and A2 groups. As an initial matter, Applicant reiterates the comments made above with respect to the term "moiety," and respectfully points out that the terms "heteroaromatic moiety" and "aromatic moiety" are clearly defined in the specification (see page 12, paragraphs [0023] and [0024] of the application as filed). Nevertheless, in order to expedite prosecution of this case, Applicant has removed the term "moiety" from the claims and requests that the rejection be removed.

The Examiner further states that the specification does not describe groups "such as synthetic polymers comprising repeat polypeptide units or any other proteins, a polymer of PEG that increases the serum half-life, or any other type of peptide or peptide-like molecules or compounds." Applicant is unsure why the Examiner has chosen to list such groups in a written desciption rejection, as these groups are not recited in the instant claims.

The Examiner asserts that "description of glycans, oligosaccharides is not sufficient to encompass numerous other pharmaceutically useful group that belongs to the same genus." Applicant respectfully submits that the term "pharmaceutically useful group" is not recited in the instant claims, so that the Examiner's remark is not relevant to the presently claimed genus. Applicant requests that the rejection be removed.

The Examiner appears to consider the "peptide" element of the claims to lack sufficient written description. The Examiner states that "there are varying lengths, varying amino acid compositions, [. . .] the number of possible sequences a peptide or protein compounds having pharmaceutical activity is vast," and "if a peptide is described only by a funtional characteristic, without any disclosed correlation between function and structure of the sequence, it is 'not [a] sufficient [identifying] characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence' MPEP 2163." As an initial matter, and as explained in the response dated December 17, 2008, the present claims are drawn to methods of peptide ligation, not peptides having a certain activity. While the Examiner asserts "there is no disclosure of a correlation between function and structure of the compounds," Applicant respectfully submits that such disclosure is unnecessary because Applicant is neither claiming compounds nor compound function. The only relevant correlation is that the peptides are all amenable to *being produced by* the claimed method.

Applicant has demonstrated that the claimed *methods* are useful to ligate a variety of peptide acyl donors with peptide amine acceptors, each having varying amino acid sequences and/or different A1 and A2 groups. While the Examiner is of the opinion that "the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives," Applicant respectfully submits that the polyfunctionalized peptides display more than sufficient variety of peptide sequence and functionalization. In fact, the Examiner has previously agreed with this point on two occasions

in stating "the polyfunctionalized peptides produced are patentably independent and distinct peptides since the structures are different" (see Office Actions dated September 17, 2008 and March 31, 2008). Therefore, it is respectfully submitted that Applicant has disclosed sufficient variety of species to satisfy the written description requirement. Applicant requests that the rejection be removed.

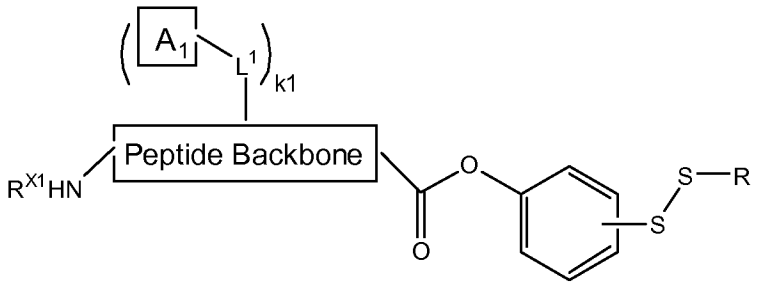
Applicant respectfully submits that the scope sought by the present claims is not unreasonable given Applicant's disclosure, particularly in view of other patents issued on similar technologies. Applicant reminds Examiner of claim 1 of the '106 patent (see above), drawn toward a method of cleaving a peptide from solid phase to produce alpha thioesters. The disclosure of the '106 is no broader than Applicant's disclosure, and yet the Examiner allowed claims encompassing *any* peptide. Other patents allowed by the Examiner reciting product-by-process or method claims that comprise modifying or derivatizing peptides include U.S. Pat. Nos. 7,524,813, 7,385,028, and 7,341,874.

Furthermore, a *peptide* is a compound of *known structure* (*i.e.*, amino acids linked together via a peptide bond). Thus, the Examiner is incorrect when she states that "the claims do not describe a single structural feature."

For all of the reasons discussed above, Applicant respectfully submits that the written description requirement is met for the claimed invention, and Applicant requests that the rejection be removed.

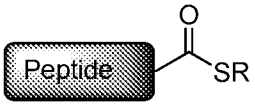
3. **Rejection under 35 U.S.C. § 102(b).** Claims 1, 3-4, 8-9 and 21 are rejected under under 35 U.S.C. § 102(b) as being anticipated by Bertozzi *et al.* (*Science*, 23 March 2001, 291: 2357-2364). The Examiner finds that the Bertozzi reference ("Bertozzi") teaches "glycoprotein synthesis by convergent coupling of glycopeptide fragments" and that "the COOH-terminal thioester can be interpreted as a disulfide substituted aryl moiety." Applicant respectfully disagrees.

Applicant respectfully submits that the peptide acyl donor of amended claim 1 is of the formula:



COOH-terminal ester

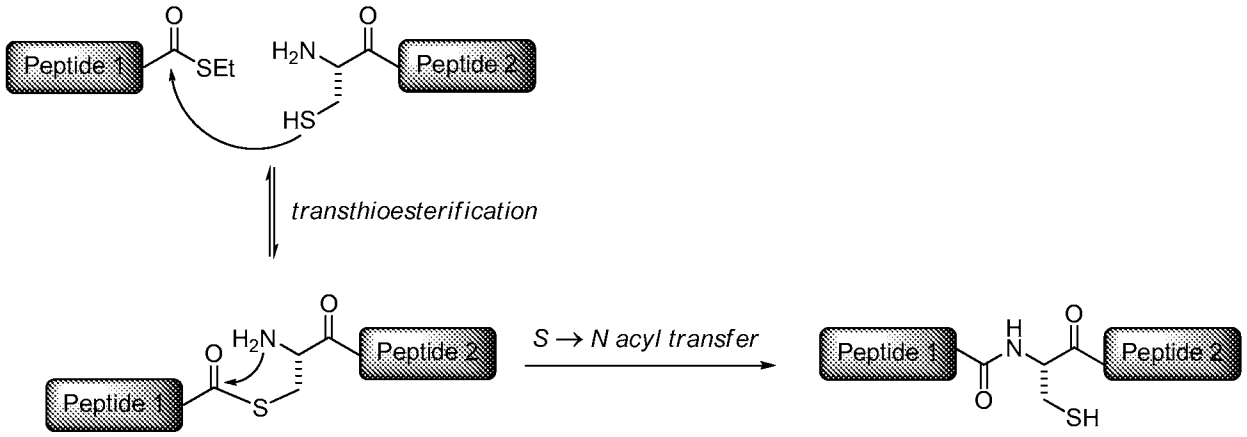
Bertozzi teaches a peptide acyl donor of the formula:



COOH-terminal thioester

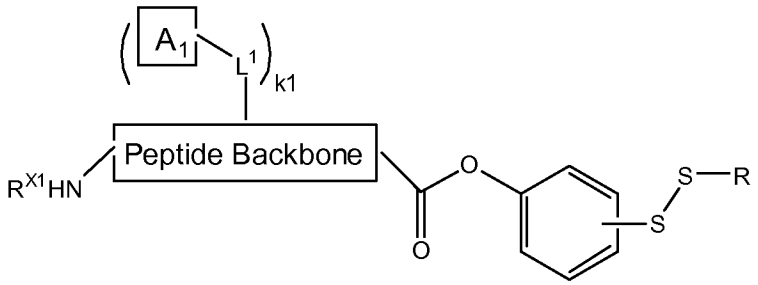
Thus, there is no possible way to interpret the thioester taught by Bertozzi as a disulfide substituted aryl group of claim 1 because the latter is connected to the peptide via an ester, not a thioester. Applicant requests that the rejection be removed.

The Examiner states that "because the in situ intermediate formed would inherently have the oxygen-substituted aryl moiety when reacted with an amine acceptor, this reference anticipates claims 1, 3-4, 8-9, and 21." Applicant assumes that in order for this to be an anticipation rejection, the Examiner is referring to the *in situ* intermediate of Bertozzi. However, the *in situ* intermediate of Bertozzi does not comprise an oxygen-substituted aryl moiety. Rather, both the peptide acyl donor and *in situ* intermediate of Bertozzi contain a thioester:



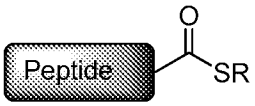
Because the instantly claimed method utilizes a peptide acyl donor comprising a COOH-terminal *ester*, and not a *thioester*, the ligation method taught by Bertozzi does not teach all of the claimed limitations and therefore cannot anticipate the instant claims. Applicant respectfully requests that the rejection be removed.

4. **Rejection under 35 U.S.C. § 103(a).** Claims 1, 3-4, 8-15, and 20-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hojo *et al.* (*Tetrahedron Letters*, 2003, 44: 2961-2964) in view of Miller *et al.* (*Angew. Chem. Int. Ed.*, Jan. 27, 2003, 42(4): 431-434). Specifically, the Examiner states that "both Hojo et al and Miller et al teach the active method steps of the instant claims [. . .] the COOH-terminal thioester can be interpreted as a disulfide substituted aryl moiety." Applicant respectfully disagrees. As stated above, the peptide acyl donor of amended claim 1 is of the formula:



COOH-terminal ester

Hojo *et al.* ("Hojo") and Miller *et al.* ("Miller") teach a peptide acyl donor of the formula:



COOH-terminal thioester

Thus, there is no possible way to interpret the thioester taught by Hojo and Miller as a disulfide substituted aryl group of claim 1 because the latter is connected to the peptide via an ester, not a thioester. Additionally, as shown above for Bertozzi, the *in situ* intermediates of Hojo and Miller contain a thioester. Applicant respectfully submits that because the combination of Hojo and Miller do not arrive at the claimed invention, the question of whether the skilled artisan would be motivated to combine the references is moot. Applicant requests that the rejection be removed.

5. **Objection under 35 U.S.C. § 112.** The Examiner states that "the specification is objected to for the following: the specification indicates 'incorporation by reference' of certain documents." In particular, the Examiner points to paragraph [0079] of the specification for a listing of small molecules drugs and publications "Pharmaceutical Substances: Syntheses, Patents, Applications" by Axel Kleemann and Jurgen Engel, Thieme Medical Publishing, 1999 and the "Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals", Edited by Susan Budavari *et al.*, CRC Press, 1996. The Examiner considers such references to be "essential" to provide a written description of the claimed invention and the manner and process of making and using it, *etc.* On what grounds has the Examiner established this material as being "essential" to the claimed invention? Applicant respectfully disagrees with the Examiner's characterization of such material as "essential." The references cited by the Examiner are well known and contain material that is known in the art. A specification need not describe—and best omits—that which is well-known in the art. See In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991) and MPEP 2163.07(b). Applicant respectfully requests that the objection be removed.

6. Miscellaneous

The Examiner indicates that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action. Although the Examiner made the restriction requirement final, Applicant submits that the withdrawn claims will be subject to rejoinder upon the Examiner's finding of an allowable generic claim from which claims to the nonelected invention depend (37 CFR 1.142(b) and MPEP 821.04).

Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Applicant thanks the Examiner for careful consideration of this case. Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

Dated: June 1, 2009

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